Cell Stress & Chaperones (2004) **9** (1), 1–3

Article no. csac. 2004.

Introducing Professor Stuart Calderwood, Stress Response Translational Research Section Editor

Lawrence E. Hightower, Editor-in-Chief

Dear Colleagues

It is a pleasure to announce the opening of a new dedicated section in *Cell Stress & Chaperones*, Stress Response Translational Research, and to introduce our founding section editor, Dr Stuart Calderwood. Stuart became Associate Professor in Radiation Oncology at Harvard Medical School in 1993 and Professor of Medicine at Boston University in 2002. He studied biochemistry at the University of Wales. His PhD thesis was a study of the role of the heat shock response in the processes of cell proliferation (Dickson and Calderwood 1976). He next studied at Stanford University the interaction of the heat shock response with cell signaling processes that lead to activation of Hsp transcription or cell death (Calderwood and Hahn 1983; Calderwood et al 1987). Dr Calderwood moved to the Dana Farber Cancer Institute, Harvard Medical School in 1985, where he continued to work on the regulation of the heat shock response, focusing on heat shock transcription factor 1 (Hsf1) in its role as both activating transcription factor and gene repressor (Price and Calderwood 1991; Chu et al 1996; Wang et al 2003; Xie et al 2003). He is currently applying our understanding of Hsf-Hsp regulation to new approaches to treat cancer through the development of small-molecule inhibitors of molecular chaperone expression and function (Asea et al 2000; Lepchammer et al 2002) and studying the role of Hsp70 in antigen presentation and anticancer vaccine development (Asea et al 2000). In 2002, Dr Calderwood became director of the Center for Molecular Stress Response at Boston University School of Medicine, a center created with the purpose of advancing understanding of the role of Hsp-Hsf in multiple disease types. The center is currently collaborating with groups in cardiology, neurology, and nephrology while maintaining Dr Calderwood's prevailing interest in approaches to cancer treatment based on the heat shock system. In 2004, Dr Calderwood will become the chief of the Division of Molecular and Cellular Radiation Oncology at The Beth Israel Deaconess Medical Center, Harvard Medical School, with the mission of pursuing Hsp-targeted drug development and vaccine design studies to the clinical trial stage. He will also continue his long-term effort to understand the physiological functions and regulatory mechanisms of the heat shock system.

What is translational research and how will it be represented in our journal? Just this year, the *Journal of the American Medical Association* (*JAMA*) introduced a new section entitled Translational Medical Research. In an editorial introducing the new section, Fontanarosa and DeAngelis (2003) stated that ''This section is intended to provide a forum for publication of basic science and translational research studies, with emphasis on studies of novel discoveries that advance the understanding of disease mechanisms and provide insights that may prove helpful in improving the diagnosis, treatment, and prevention of common diseases and conditions.'' They indicated that *JAMA* rarely sees articles from basic science investigations or preclinical translational research. Our journal also is incomplete but from the opposite direction. Rarely do we see clinical research. The statement of purpose for translational research in *JAMA* is broad, as befits a general medical journal, but it can work for *Cell Stress & Chaperones* as well if we qualify it to focus on cellular stress response research, as befits a specialty journal. Translational research is often described as a research approach that extends from laboratory bench to patients' bedsides in both directions, ie, a translational research highway of sorts. Most descriptions make the point that the best translational research begins with a significant clinical problem, to which basic science techniques and thinking are applied, which in turn results in new ideas on how to solve the clinical problem. This can be envisioned as a cycle that gains power with each successful turn. To make the cycle work requires close collaborations among basic scientists and clinicians. Colleagues with MD and PhD degrees are seen as particularly valuable in powering the cycle because they speak the language of both the clinic and the research laboratory, a linguistic

component of translational research the value of which should not be underestimated.

We are very fortunate to have editors and regular reviewers for our journal who are practicing physicians, basic research scientists, and a few who are both. I think it reflects the appreciation in both groups of the potential of the cellular stress response field to reveal new molecular mechanisms as well as solve clinical problems. This is not necessarily the norm for specialty journals, and it is not easy coverage to attain in the present research climate. Rosenberg (1999) wrote an article a few years ago entitled ''Physician-Scientists—Endangered and Essential,'' in which he presented data showing a dramatic decline in the number of individuals with MD degrees who were first-time applicants for National Health Institutes grants and showing no increase in this metric for those with MD or PhD degrees. In a more recent article about careers in translational clinical research, Nathan (2002) opened by noting a recent survey showing that only 11% of medical school graduates are planning careers that can be described as research oriented or even having a significant research component. It is no wonder that few research groups exist that can drive the length of the translational highway, and few journals are equipped to cover the trip.

What can we at *Cell Stress & Chaperones* realistically hope to accomplish to foster translational research? I think that we can increase the traffic on the translational highway in our research field by encouraging the submission of papers using cultured human cells and tissues in the study of the cellular physiology of stress responses, those using animal models for human diseases, and those using human populations for studies of stress responses to environmental conditions and diseases. At first, there may be very few articles that ''translate'' between these systems, but having this mix of articles in the same journal may stimulate more ''translational thinking'' among our readers, reviewers, and authors.

Half the articles in the present issue are studies of humans or their cells or genes, demonstrating that our journal is already a welcoming environment for the kinds of translational research just described. Here is a sampling. Beedholm et al (2004) used human skin fibroblasts at different passage levels in culture as a model to study the effects of repeated mild heat shock on proteasomes. They found increased proteasomal activity in early- and mid-passage cultures but a lower responsiveness in late-passage senescent cells. It was proposed that the stimulation in earlier-passage cells is due to induction and increased binding of proteasomal activators and not to increased cellular content of proteasomes. Readers will find in the same issue one of the few studies of stress protein levels in human populations grouped by age (Jin et al 2004). In a healthy human population, serum Hsp70 levels increased with age in individuals between 15 years and 30 years of age, but the correlation turned negative in individuals aged between 30 and 50 years. In a parallel study of lymphocyte Hsp70, levels were negatively correlated with age in individuals over 40 years of age. The authors concluded that age is a significant variable to be considered when serum and lymphocyte Hsp70 levels are used as biomarkers to evaluate disease and exposure to environmental stresses in human populations. In one of the broadest studies to date of human heat shock promoters, Trinklein et al (2004) evaluated the binding of Hsf1 and Hsf2 at the promoters of 32 heat shock genes in a human erythroleukemic cell line. They were able to identify new Hsf1-binding sites near genes known previously to be heat inducible. In addition, they showed that Hsf1 binding is activated more by heat than by hemin, whereas Hsf2 binding to the same targets is activated only by hemin. Animal models remain essential in translational research. Carbon tetrachloride–treated rats are a broadly used model system for toxicant-induced liver damage. Carbon tetrachloride causes both necrotic and apoptotic cell death in damaged liver tissue. Lee et al (2004) now report that cytosolic molecular chaperones are induced in the livers of rats treated with this toxicant. Furthermore, liver damage is much reduced in rats that have been stress conditioned using heat. Stress conditioning is very likely to translate into the clinic some day and has been discussed in detail by one of our editorial board members, Perdrizet (1997).

We anticipate that the new section on Stress Response Translational Research will help *Cell Stress & Chaperones* to fulfill its vision statement to become a comprehensive journal of stress biology and medicine. I note also that one of the stated aims of the journal's owner, The Cell Stress Society International, is to promote the clinical and industrial applications of basic research in the field. Manuscripts for this or any other section of *Cell Stress & Chaperones* can now be submitted electronically at our new website http://cellstress.allentrack.net.

REFERENCES

Asea A, Ara G, Teicher BA, Stevenson MA, Calderwood SK. 2001. Effects of the flavonoid drug quercitin on the response of human prostate tumors to hyperthermia in vivo. *Int J Hyperth* 17: 347–356.

Asea A, Kraeft S-K, Kurt-Jones EA, Stevenson MA, Chen LB, Finberg RW, Koo GC, Calderwood SK. 2000. HSP70 stimulates cytokine production through a CD14 dependent pathway, demonstrating its dual role as a chaperone and cytokine. *Nat Med* 6:435–443.

Beedholm R, Clark BFC, Rattan SIS. 2004. Mild heat stress stimulates 20S proteasome and its 11S activator in human fibroblasts undergoing aging in vitro. *Cell Stress Chaperones*, 9:49–57.

Calderwood SK, Hahn GM. 1983. Thermal sensitivity and resistance of insulin binding. *Biochem Biophys Acta* 756:1–8.

Calderwood SK, Stevenson MA, Hahn GM. 1987. Heat stress stim-

ulates inositol trisphosphate release and phosphorylation of phosphoinositides in CHO and Balb C 3T3 cells. *J Cell Physiol* 130:369–378.

Chu B, Soncin F, Price BD, Stevenson MA, Calderwood SK. 1996. Sequential phosphorylation of heat shock factor-1 by MAP kinase and glycogen synthase kinase 3 represses transcriptional activation of the heat shock protein seventy promoter. *J Biol Chem* 271:33470–33480.

Dickson JA, Calderwood SK. 1976. *In vivo* hyperthermia of Yoshida tumour induces entry of non-proliferating cells into cycle. *Nature* 263:772–774.

Fontanarosa PB, DeAngelis CD. 2003. Translational medical research. *JAMA* 289:2133.

Jin X, Wang R, Xiao C, et al. 2004. Serum and lymphocyte levels of Hsp71 in aging: a study in the normal Chinese population. *Cell Stress Chaperones,* 9:69–75.

Lee K-J, Terada K, Oyadomari S, Inomata Y, Mori M, Gotoh T. 2004. Induction of molecular chaperones in carbon tetrachloride-treated rat liver: implications in protection against liver damage. *Cell Stress Chaperones,* 9:58–68.

Lepchammer S, Asea A, Mallick R, Zhong R, Sherman MY, Calderwood SK. 2002. Development of an XTT tetrazolium based assay for detection of specific hyperthermia sensitizers in a high flux screening program. *Int J Hyperth* 18:203–215.

Nathan DG. 2002. Careers in translational clinical research—historical perspectives, future challenges. *JAMA* 287:2424–2427.

Perdrizet GA. 1997. *Heat Shock Response and Organ Preservation: Models of Stress Conditioning*. RG Landes Co, Austin, TX.

Price B, Calderwood SK. 1991. Ca++ is essential for multistep activation of the heat shock factor in permeabilized cells. *Mol Cell Biol* 11:3305–3368.

Rosenberg LE. 1999. Physician-scientists—endangered and essential. *Science* 283:331–332.

Trinklein ND, Chen WC, Kingston RE, Myers RM. 2004. Transcriptional regulation and binding of Hsf1 and Hsf2 to 32 human heat shock genes during thermal stress and differentiation. *Cell Stress Chaperones,* 9:21–28.

Wang Z, Grammatikakis N, Siganou A, Calderwood SK. 2003. Regulation of molecular chaperone gene transcription involves the serine phosphorylation, 14-3-3e binding and cytoplasmic sequestration of heat shock factor 1. *Mol Cell Biol* 23:6023–6026.

Xie X, Zhong R, Chen C, Calderwood SK. 2003. Heat shock factor 1 contains two functional domains that mediate transcriptional repression of the *c-fos* and *c-fms* genes. *J Biol Chem* 278:4687–4698.